

EFFECTS received a final rejection, and a PCT application, PCT/US98/19429, entitled A DELIVERY OF ARGININE TO CAUSE BENEFICIAL EFFECTS is being prosecuted currently. All of these cases contain almost identical disclosures to the instant application with respect to the use of an hostile biophysical environment.

It is apparent from the Examiner's comment "...nor is it clear what a hostile biophysical environment might embrace..." that a clarification of the central aspect of the present invention may be useful as a preface to the Examiner's substantive rejections. The claims of the present invention are limited to a topical delivery vehicle for L-arginine. L-arginine hydrochloride provides a precursor to the molecule nitric oxide, NO. NO is the substance that relaxes the blood vessels, allowing for increased blood flow. The concentration of the L-arginine based compound, e.g., L-arginine hydrochloride, is preferably between 0.25 to 25% w/v.

Choline chloride, sodium chloride and magnesium chloride are non-limiting examples of salts which provide a high ionic strength environment for the highly charged molecule, L-arginine. This high ionic strength environment is an example of an hostile biophysical environment for L-arginine. That is, the highly charged ionic strength provided by the salts to the L-arginine carrier is an unfavorable environment for the highly charged L-arginine which facilitates or promotes L-arginine migration out of the carrier and into a more hospitable, less charged environment such as human tissue. The ionic strength is preferably any amount greater than two times the physiological ionic strength of blood.

Thus, the topical delivery vehicle containing the nitric oxide releasing substance, choline chloride, sodium chloride and/or magnesium chloride is the agent which produces the beneficial effects such as hair growth, healing of ulcers or restoration of normal erectile function in males suffering from erectile dysfunction.

35 USC §112 Second Paragraph Rejections

Claims 33-60 have been rejected under 35 USC §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In making this rejection, the Examiner states:

It is not clear whether or not the materials in claim 39 and 47, etc. are meant to be used as alternatives or in combination since this is not stated in the claim.

Claim 39 as written is dependent on claim 33. Claim 39 is very specific as to what the delivery vehicle is. This claim is neither in the alternative, nor is it in combination. The words "or" and "combine" do not appear in this claim. Please note the term "wherein" is used in this dependent claim. Therefore, the basis of this rejection is not understood. Applicant respectfully requests withdrawal of this rejection.

Similarly, withdrawal of the rejection of claim 47 is also requested. Claim 47 as written is dependent on claim 42. As discussed *supra*, claim 47 is also very specific as to what delivery vehicle is being used to create the hostile biophysical environment. This claim is neither written in the alternative, nor does the

applicant wish to imply the combination of materials. The claim should be interpreted literally. Therefore, withdrawal of this rejection is respectfully requested.

Applicant notes the Examiner's comment:

It is not clear if the concentration of ionic salt sufficient to create an ionic environment which causes a substance to migrate from the vehicle to the skin embraces zero concentrations of salt in that there is no reason why nitric oxide releasing substances cannot be absorbed by the skin even in the absence of salt.

While it is true that nitric oxide substances can be absorbed by the skin in the absence of salt, the Applicant's use of a high ionic biophysical environment in the delivery vehicle increases the efficiency of the absorption of L-Arginine into tissue. As has been stated previously, one approach to effectuate absorption of a highly charged molecule such as L-arginine into tissue is to create a biophysically hostile environment in the delivery vehicle such that L-arginine would prefer to be in the tissue. Clearly, zero concentrations of salt would not work in a delivery mechanism that uses a high ionic strength to force the L-arginine out of the delivery vehicle and into tissue. Applicant, has found that the high salt hostile biophysical environment is the simplest and most efficient delivery mechanism for facilitating the absorption of L-arginine into tissue. For this reason, the claims of the instant invention teach the use of a high ionic strength environment. As the Examiner knows, an invention that increases the efficiency of a process described in prior art is patentable. Therefore, Applicant respectfully requests that this rejection be withdrawn.

35 USC §112 First Paragraph Rejections

Claims 35-38,44 and 53-55 have been rejected under 35 USC §112 first paragraph, as based on a disclosure which is not enabling. In making this rejection the Examiner States:

There is nothing in the specification which discloses a combination of a hydrophobic delivery vehicle and an ionic salt. Note in this regard page 7 of the specification discloses that alternatively a hostile biophysical environment may be created by placing the highly charged L-arginine in an hydrophobic, oily environment such as in an oil-based cream containing little or no water. It is therefore clear that use of the hydrophobic vehicle is an alternative to the salt containing vehicles. Any claims reciting the limitation containing the hydrophobic delivery vehicle in combination with an ionic salt therefore lack support in the specification as filed and such limitation is new matter. Furthermore, salts in general are not soluble in hydrophobic delivery vehicles and it is not clear how the method of for instance claim 35 could be conducted which is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure.

In contrast to the Examiner's assertion that the instant invention as claimed is not enabling, the Applicant respectfully points out that the specification repeatedly discloses the use of an hostile biophysical environment for L-arginine created by a high salt concentration and a delivery vehicle which is a penetrating base cream. Specifically on page 3 of the Applicant's disclosure under Summary of the Invention, it states: "In one embodiment of the invention, a penetrating cream containing L-arginine at an effective concentration and a salt, such as sodium chloride, at a concentration sufficient to create a hostile biophysical environment for the L-arginine in the cream is applied nightly to the scalp..."

Furthermore, on page 4 of the specification under Detailed Description of the Invention, the specification again discloses the combination of the hydrophobic delivery vehicle and the ionic salt where it states:

“The preferred embodiment consists of a base cream with the properties of excellent absorption into the skin which also includes L-arginine hydrochloride...The components of the base cream may be those commonly found in hand creams, such as water, mineral oil, glyceryl sterate...” Clearly, some of the ingredients of the base cream are hydrophobic. It is well known in the chemical arts that salts can be coupled with hydrophobic creams. In fact, topical delivery of the L-arginine salt would not be possible without the base cream delivery vehicle as taught in the instant invention. Thus, the claims as submitted are enabling and have support in the specification. Therefore, withdrawal of this rejection is respectfully requested.

35 USC § 102 Rejections

It is particularly apparent from the prior art cited by the Examiner that it is known that the introduction of nitric oxide in the body produces desirable effects, including penile erection, hair growth muscle relaxation and increased circulation of blood flow to the surrounding tissue. Indeed, the art cited by the Examiner discloses these exact effects. It is also clear from the art cited by the Examiner that L-arginine, L-arginine salts and L-arginine derivatives are known to effectively release nitric oxide.

Specifically, the Examiner cites Weuffen et al. as disclosing a

process in which an arginine containing substance in combination with various salts are applied to the scalp to promote hair growth." However, careful reading of this reference shows that the invention uses

preparations based on alkali metal, alkaline earth metal and/or ammonium salts of thiocyanic acid and are characterized in that they contain as a further constituent, at least one component or mixtures selected from estrogens, sulfur, sulfide ions, vasodilators, skin-active vitamins, inorganic selenium compounds, amino acids and carboxylic acids physiologically occurring in the skin...See Column 3, lines 14-22 in Patent No. 5, 629,002.

Nowhere in this reference is the topical use of L-arginine discussed in conjunction with the promotion of hair growth. Instead, this reference discloses the use of thiocyanates as the active ingredient. More importantly, this reference does not disclose the use of an hostile biophysical environment as a means of facilitating the delivery of L-arginine to the tissue. It is this novel functionality of the hostile biophysical environment NO delivery system taught by the instant invention that is neither explicitly or implicitly taught or suggested in the prior art. As the examiner knows, rejections under 35 USC §102 are proper only when the claimed subject matter is identically disclosed in the prior art. Therefore, the instant invention is not anticipated by the Weuffen reference, and the applicant respectfully requests withdrawal of this rejection.

Claims 33-34 and 39 are rejected under 35 USC § 102(a) as being anticipated by Hechtman. In making this rejection the Examiner states: "Hechtman discloses a topical treatment in which L-arginine is applied to an area being treated whereby nitric oxide is released." As discussed *supra*, Applicant acknowledges that the prior

art discloses the beneficial effects of NO. Applicant is not claiming these actions.

Instead, the claims of Applicant's invention disclose a novel L-arginine delivery system for the NO precursor. Nowhere in this Hechtman reference is the creation of an hostile biophysical environment for the delivery of L-arginine disclosed. Specifically, with respect to the Examiner's comment regarding the electrolyte solution disclosed in claim 6 of the patent, Applicant notes that this electrolyte solution is not limited to an ionic strength which is high enough to create an hostile biophysical environment. Because the cited reference fails to disclose all of the material elements in a claim, Hechtman does not anticipate the instant invention. Therefore, Applicant respectfully requests withdrawal of this rejection.

35 USC § 103 Rejections

Applicant notes the Examiner's rejections of claims 33-34,38,39,51-54,56,59, and 60 as being obvious over Weuffen et al. In making this rejection, the Examiner used the identical arguments as were used in his §102 rejection of these claims. Furthermore, Applicant takes note of Examiner's §103 rejection of claims 33-34 and 39 wherein he states "or, in the alternative, under 35 USC 103(a) as being obvious over Hechtman (USP 5,595,753).

As discussed *supra*, there is nothing in either Weuffen et al. or Hechtman et al., or their combination, which either teaches or suggests either implicitly or explicitly, the use of an hostile biophysical in the delivery vehicle for the facilitation of the delivery of L-arginine into tissue. Accordingly, Applicant submits that

neither of these references renders the instant invention obvious. Applicant respectfully submits in light of the foregoing remarks, all of the claims are now in a condition for allowance. Applicant respectfully requests reconsideration.

Finally, Applicant acknowledges the request for an Information Disclosure Statement. It should be noted that during the prosecution of the above referenced application, no Information Disclosure Statement was filed with the United States Patent and Trademark Office.

Moreover, it should be noted that the undersigned attorney has asked the inventor to carefully review each of the articles cited by the Applicant in the Background of the Invention section of the specification of the instant application for relevance. The inventor has concluded that none of these references are relevant as they are all directed to background with respect to the use of NO delivery systems to cause vasodilatation. As none of these references are deemed relevant to patentability, an Information Disclosure Statement is not deemed necessary for this application. If the Examiner would like any of these non-material, background references for his own interest, the Applicant would be happy to supply them.

It should also be noted that a PCT application relating to this case was filed on September 17, 1998. This is PCT/US98/19429 entitled A DELIVERY OF ARGININE TO CAUSE BENEFICIAL EFFECTS. An International Search Report has been completed by the International Searching Authority. This report was mailed on January 11, 1999. A copy of the report and the references cited therein

are enclosed. It should be noted that Hechtman U. S. Patent No. 5,595,753 and Weuffen U.S. Patent No. 5, 629,002 cited in this report as X references were also cited by the Examiner in the November 20, 1998 office action for U.S. Ser. No. 08/932,227.

It is believed that no other fees are currently due. However, in the event of any inadvertant fee deficiency or overpayment, authorization is hereby granted to charge or credit such deficiency or overpayment to deposit account # 12-2147.

If there is any problem with this submission, or the Examiner requires further information, it is requested that the undersigned be contacted by collect phone call.

Respectfully submitted,

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Dated February 17, 1999

Certification Under 37 CFR § 1.8

I hereby certify that this Amendment and Response to the Official Action dated 11/20/98 and any document referred to therein as being attached or enclosed is being deposited with the United States Postal Service on 2/17/99 as postage pre-paid first class mail in an envelope addressed to : Assistant Commissioner for Patents, Washington, D.C. 20231.

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